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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

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22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,371	KAEMPFER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-31,47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-31,48 and 49* is/are rejected.

7)☒ Claim(s) *10 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1, 3-31 and 47-49 are pending.

Applicants' traversal, the cancellation of claim 2, the amendment to claims 1, 3-31 and 47-49, the amendment to the specification, and the Declaration under 1.132 by Raymond Kaempfer in paper no. 20 filed on 5/5/03 is acknowledged and considered.

Information Disclosure Statement

The request by the examiner for the IDS filed on 5/14/01 is moot since the applicants state that an IDS was not filed on 5/14/01. The IDS paper no. 6 filed on 5/14/01 will be removed from the application cover.

Claim Objections

Applicant's arguments, see paper no. 20, filed on 5/5/03, with respect to the objection have been fully considered and are persuasive. The objection of claims 1, 4-7, 11-31, 47-49 of has been withdrawn because of the amendment to the claims. However, new objections are required in view of the amendment to the claims 10, 21, and 47

Claim 10 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim – should refer to other claims in the alternative only --. See MPEP § 608.01(n). Accordingly, claim 10 has not been further treated on the merits.

Claims 21 and 22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 21 and 22 depend on claim 14. Claim 14 is directed to the human TNF-α gene. Claims 21 and 22 recite inserting a cis-acting element into the intron of the human TNF-α gene. However, the human TNF-alpha gene already has a cis-acting nucleotide in an exon (3'UTR) of said gene but not in an intron. If the cis-acting element is inserted into an intron of the human TNF-alpha gene than it is no longer the human TNF-alpha gene. Thus, claims 21 and 22 do not further limit the subject matter of claim 14, they are outside its scope.

Claim 47 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim 47 has not been further treated on the merits.

Claims 7, 10, and 24 are objected to because of the following informalities: The terminology "and/or" in the claims is unacceptable language.

Claim 23 is objected to because of the following informalities: The statement in claims, "**a** cis-acting nucleotide sequence according to claim 1" in claim 23 is improper format for a dependent claim. The dependent claim should state, -- **the** cis-acting nucleotide sequence according to claim 1 --.

Claims 23, 27, 48, and 49 are objected to because of the following informalities: The statement in claims, "**a** DNA construct according to claim.." in claims 23, 27, 48, and 49 is

improper format for a dependent claim. The dependent claim should state, -- **the** DNA construct according to claim... --.

Claim 28 are objected to because of the following informalities: The statement in claims, "**a** vector according to claim 23" in claim 28 is improper format for a dependent claim. The dependent claim should state, -- **the** vector according to claim 23 --.

Appropriate correction is required.

Specification

Applicant's arguments, see paper no. 20, filed on 5/5/03, with respect to the objection have been fully considered and are persuasive. The objection to the specification of has been withdrawn because of the amendment to the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 1 filed on 5/5/03 introduces new subject matter into the application. The application and the originally filed claim as a whole are directed to a cis-acting nucleotide.

The original specification did not disclose a cis-acting nucleotide that does not comprise a full-length coding region. No page was cited for support of the limitation added to the claim. It is apparent that the applicants at the time the invention was made did not intend or contemplate excluding a cis-acting nucleotide sequence comprising a full-length coding region as part of the disclosure of their invention. At the time the application was filed, there is no evidence in the specification that the applicants were relying on the specification for the limitation "the cis-acting nucleotide sequence does not comprise a full-length coding region" in claim 1 and claims dependent thereof, as it is now claimed.

Claims 1, 3, 7-9 and 11 remain and claims 4-6, 12-31, 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-9, 11-31, and 48- 49, as best understood, are readable on a genus of a cis-acting nucleotide sequence, wherein the genus of sequences is capable of rendering the removal of introns from a precursor transcript encoded by a gene, is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification described a cis-acting nucleic sequence, which is set forth in SEQ ID NO: 1 and forms a stable, 5'proximal 48-nt stem-loop containing 17 base pairs set forth in SEQ ID NO: 2 (Table 1). Furthermore, the as-filed specification contemplates biological functional fragments, derivatives, mutants and homologues of the nucleotide sequence substantially as

denoted by SEQ ID NO: 1. The disclosure provides sufficient description for SEQ ID NO: 1. However, the as-filed specification does not provide sufficient description of a genus of cis-acting nucleotide sequence.

The as-filed specification does not provide an adequate written description of a representative number of species of cis-acting nucleotide sequence. The description is considered essential and is required for an adequate description of a representative number of species as embraced by the claimed genus of cis-acting nucleotide sequence because the description is neither described sufficiently in the specification nor conventional in the prior art. A mere statement asserting that any sequence with biological functional fragments, derivatives, mutants and homologues of the nucleotide sequence substantially as denoted by SEQ ID NO: 1 or SEQ ID NO: 2, without providing the essential and specific description of a representative number of species embraced by the claimed genus does not lend evidentiary support for a skilled artisan to have recognized that applicants were in possession of the genus of cis-acting nucleotide sequence as claimed, particularly since the description of a sufficient number of nucleotide sequences of a generic cis-acting nucleotide sequence is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the representative number of species of cis-acting nucleotide sequence or nucleic acids on the basis of the only disclosure of SEQ ID NO: 1 and SEQ ID NO: 2.

The guidance in the specification is not sufficient to support the present claimed invention directed to the genus of cis-acting nucleotide sequence. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of

applicant's effective filing date. Claiming a genus of cis-acting nucleotide sequence that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of cis-acting nucleotide sequence that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 5/5/03 have been fully considered but they are not persuasive. The specification contemplates a genus of cis-acting nucleotide sequences. The specification provides sufficient guidance and/or factual evidence for SEQ ID NO: 1 and SEQ ID NO: 2 (fragment of SEQ ID NO: 1). However, the specification does not disclose that a cis-acting nucleotides other than SEQ ID NO: 1 and fragment of SEQ ID NO: 1 are capable of the removal of introns from a precursor transcript encoded by any gene dependent upon activation of

a trans-acting factor, said trans-acting factor being PKR which is capable of phosphorylating the alpha subunit of EIF-2. The polynucleotide sequences embraced by the genus are potentially enormous and the specification does not provide sufficient description for a representative number of species. The species within a genus of cis-acting nucleotides widely varies. For example the art of record, at the time the application was filed, and the as-filed specification teach that SEQ ID NO: 1 and SEQ ID NO: 2, poxvirus A-type inclusion, eukaryotic nuclear gene from mammalian factor VIII, collagen, alpha- and beta-globin (See Mehtali, US Patent 6,399,587) are cis-acting nucleotide sequences and only SEQ ID NO: 1 and SEQ ID NO: 2 can remove the introns from a precursor transcript encoded by any gene dependent upon activation of a trans-acting factor, said trans-acting factor is PKR which phosphorylates the alpha subunit of EIF-2a. In view of art of record and the reasons set forth above it is apparent that the function and structure of the different polynucleotides within each species embraced by the genus vary considerably. The only cis-acting nucleotides (SEQ ID NO: 1 and SEQ ID NO: 2) that are disclosed in the specification are the only nucleotide sequences that meet the functional characteristics described in the claims. The specification does not disclose that the structure of SEQ ID NO: 1 or 2 correlates to a genus of the claimed cis-acting nucleotide sequences. There is no structural function relationship to being a cis-acting nucleotide sequence and meeting the functional characteristics set forth in the claims. Thus, the specification does not provide adequate written description for the claimed genus of cis-acting nucleotide sequences.

The statement, "the specification provides methods of evaluating potential sequences having the claimed function in the examples," indicates that the applicants were not in

possession of a sufficient number of species to representative the claimed genus of cis-acting nucleotide sequences.

The Declaration under 37 CFR 1.132 filed by Raymond Kaempfer is insufficient to overcome the rejection of claims based upon 112 first paragraph written description as set forth in the last Office action because: of the reason set forth above.

In addition, with respect to argument that the post-filed publication, Ben-Asouli et al., Cell, Vol. 108, 221-232, 2002, (published four years after the foreign application was filed) listing five authors (2 are inventors for the instant application) teaching the discovery of two additional 2-APRE elements derived from two different genes, beta-globin and human IFN-gamma (exhibit B). The argument is not found persuasive because the article does not use the methods and materials taught in the specification. The specification describes a cis-acting nucleotide sequence in the 3' UTR of the human TNF-alpha gene. The novel genes discovered in the article have no structural feature (sequence homology) in common with the cis-acting element of the TNF-alpha gene (as pointed out by Professor Kaempfer, see page 5 of Declaration). In view of the article, the article supports the written description rejection because the genes used in the articles display that there is no known or disclosed correlation between the cis-acting nucleotide sequence set forth in SEQ ID NO: 1 and the cis-acting elements in the IFN-gamma and beta-globin. The specification does not describe a structure that would provide sufficient guidance for the cis-acting elements in the two different genes. The physical and chemical properties of the genes are distinct from the human TNF-alpha gene and description for either gene is provided in the specification. Thus, one skilled in the art at the time the invention

was made would not have recognized that applicants were in possession of the claimed invention as presently claimed.

Claims 1, 3, 7-9, and 11 remain and claims 5, 6, 12-31, 48, and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cis-acting nucleotide sequence comprising the 3' untranslated region of the human tumor necrosis factor alpha gene set forth in SEQ ID NO: 1 or consisting of SEQ ID NO: 2, which removes intron(s) from a pre-cursor transcript encoded by a gene, wherein said gene comprises at least one of said cis-acting nucleotide sequence and is dependent upon activation of a trans-acting factor, wherein said trans-acting factor is the RNA-activated protein kinase (PKR), which phosphorylates the alpha subunit of eukaryotic initiation factor 2 (eIF2), and does not reasonably provide enablement for a cis-acting nucleotide which is capable of rendering the removal of introns from a precursor transcript encoded by any gene, which harbors such cis-acting nucleotide sequence, occurring the production of mRNA of said gene, dependent upon activation of a trans-acting factor, wherein said trans-acting factor being the RNA-activated protein kinase which is capable of phosphorylating the alpha subunit of EIF-2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of cis-acting nucleotide sequence) as recited in the claims, particularly in

view of the reasons set forth above, one skilled in the art would not have known how to make and use the claimed invention so that it would operate as intended, e.g. capable of rendering the removal of intron(s) from a pre-cursor transcript encoded by a gene.

The claimed invention encompasses modulating gene expression using a cis-acting nucleotide sequence, which renders the removal of introns from pre-cursor transcript encoded by a gene of interest. The field of the invention lies in nucleotide sequences that could be used as cis-acting nucleotide sequence, e.g. TNF-alpha 3'UTR.

The as-filed specification teaches that the cis-acting element in the human TNF-alpha 3'UTR renders splicing of TNF-alpha mRNA sensitive to inhibition by 2-Aminopurine (AP), and contemplates that this is a unique and novel tool for bringing expression of a desired gene under the control of this mechanism. The state of the art exemplified by Jarrous teaches a method of regulating gene expression at the mRNA level transforming a host cell with a vector comprising the TNF-alpha gene, including the 3' untranslated region, wherein the activity of the RNA activated eIF2alphakinase in the host cells is modulated by the use of 2-AP (IDS, page 2820, column 1, lines 5-24). Jarrous further teaches that:

> Most likely, regulation by 2-AP is mediated through a particular sequence within the TNF-alpha primary transcript to produce general inhibition of the splicing of this transcript (page 2821).
>
> Deletion of a particular sequence from the TNF-alpha gene renders splicing of the encoded pre-cursor transcripts resistant to inhibition by 2-AP, while introduction of said

sequence into the TNF-beta shifts inhibitory effect of 2-AP on the TNF-beta gene expression from transcription to splicing (page 2821).

The as-filed specification locates the sequence through genetic techniques that Jarrous speculates about in the TNF gene (see pages 26-41).

In view of the In re Wands Factors, the claimed invention is only enabled for cis-acting nucleotide sequence set forth in SEQ ID NO: 1 and SEQ ID NO: 2 and is not enabled for the full breath of the claimed invention. The claimed invention is broader (biologically functional fragments, derivatives, mutants and homologues of the nucleotide sequence set forth in SEQ ID NO: 1, sequences whose complementary sequence hybridizes under conditions which allow for such hybridization to occur, or **derived** from the 3' untranslated region of human tumor necrosis factor alpha gene) than the enabling disclosure because there is no guidance as to which amino acids of the nucleotide sequence set forth in SEQ ID NO: 1 or 2 may be changed while cis-acting activity is retained. The state of the art (IDS, Jarrous et al., Molecular and Cellular Biology, Vol. 16, 1996, 2814-2822) teaches that two genes (TNF-beta and IL-1beta) have a similar sequence to TNF alpha and do not show that 2-AP blocks their mRNA unlike TNF-alpha (page 2814). In view of the art of record, it would require undue experimentation for one skilled in the art to arrive at other sequences that are cis-acting nucleotide sequences. In Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences with a particular function that needs to be determined subsequence to the construction of the sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitation of the claim are disclosed and if undue experimentation would be required for one skilled in the art for

the determination of other sequences that are embraced by the claims. If it would require undue experimentation to identify other sequences that have cis-acting activity, it certainly would require undue experimentation to make the genus of cis-acting nucleotide sequences. This is the case here. Therefore, it would be reasonable to conclude that it would require undue experimentation to make the entire scope of the claimed invention.

In addition, with respect to claims 4, 5, 8, and 9 embracing sequences whose complementary sequence hybridizes under conditions, which allow for such hybridization to occur, with the nucleotide sequence of a) or b). The claimed invention fails to provide sufficient guidance for one skilled in the art to practice the full breadth of the claim because one skilled in the art would be able to use SEQ ID NO: 1 or 2 to probe for sequences that completely complement SEQ ID NO: 1 or 2. However, a nucleotide sequence whose complementary nucleotide sequence hybridizes with biologically functional fragments, derivatives, mutants and homologues of the nucleotide sequence substantially as denoted by SEQ ID NO: 1 comprises an enormous number of nucleotide sequences that would not meet the structural and/or functional limitation of claims. Furthermore, the nucleotide sequences encompass any nucleic acid sequence (e.g., 10 nucleotides to 1,000 nucleotides) that would not have cis-acting activity and the as-filed specification does not provide sufficient guidance for one skilled in the art to reasonably determine which nucleotide sequences have cis-acting nucleotide activity. Therefore, it would take one skilled in the art an undue amount of experimentation to make and/or use claimed sequences whose complementary sequence hybridizes under conditions, which allow for such hybridization to occur, with the nucleotide sequence of a) or b).

Furthermore, with respect to using a trans-acting factor in claims 1, 3-9,11, wherein said trans-acting factor is an RNA-activated protein kinase which is capable of phosphorylating the alpha-subunit of eIF2, the as-filed specification only provides sufficient guidance for one skilled in the art to use PKR (pages 21-22) and not for the full breadth of the claimed RNA-activated kinases which is capable of phosphorylating the alpha-subunit of eIF2. The state of the art teaches that two types of kinases (PKR and heme) that are capable of phosphorylating the alpha-subunit of eIF2 (IDS, Jarrous, page 2814, 1996). However, the as-filed specification does not provide sufficient guidance for one skilled in the art to reasonably determine if heme kinases can be used in the claimed product. Jarrous teaches that, "Both activations of PKR and its inhibition require highly ordered RNA structures rather than specific sequences (IDS, Osman et al., Genes & Development, Vol. 13: 32980-3293). The art of the record and the as-filed specification fail to provide sufficient guidance for one skilled in the art to reasonably determine whether heme kinases share a similar high ordered RNA structure. Therefore, it is not apparent that heme kinases could be used as a trans-acting factor for the claimed cis-acting nucleotide sequence. Thus, the claimed invention is only enabled for using PKR as the trans-acting factor.

In conclusion, in view of the In Re Wands Factors, the claimed invention is only enabled for a cis-acting nucleotide sequence comprising the 3' untranslated region of the human tumor necrosis factor alpha gene set forth in SEQ ID NO: 1 or consisting of SEQ ID NO: 2, which removes intron(s) from a pre-cursor transcript encoded by a gene, wherein said gene comprises at least one of said cis-acting nucleotide sequence and is dependent upon activation of a trans-acting factor, wherein said trans-acting factor is the RNA-activated protein kinase (PKR), which capable of phosphorylating the alpha subunit of eukaryotic initiation factor 2 (eIF2)and not for

the full scope of the claimed embodiment. It is not apparent how one skilled in the art can make and/or use the genus of cis-acting nucleotide sequences, given that unpredictability of identifying a cis-acting nucleotide with the claimed limitations and the lack of guidance provided by the specification. Therefore, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of reasonably extrapolate from SEQ ID NO: 1 or 2 to the claimed genus of cis-acting nucleotide sequences.

Applicant's arguments filed 5/5/03 have been fully considered but they are not persuasive. Since the arguments provided by the applicants are directed to both the 112 first paragraph written description and enablement, the rejections of record are maintain for the same reasons as set forth under the written description.

Furthermore, with respect to the assertion by the applicants that the post-filing article (Exhibit B) teaches that the specification provided sufficient guidance for one skilled in the art to make and/or use the full scope of the claimed invention.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment…; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d…[1557], 1562, 27 USPQ2d…[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in

view of the art of record exemplifying the unpredictability of making and/or using any cis-acting

nucleotide sequences, for those skilled in the art to experiment with any nucleotide sequence to produce a cis-acting nucleotide sequence as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for a representative number of cis-acting nucleotide sequences, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the cis-acting element (SEQ ID NO: 1 or 2) taught in the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed invention.

The Declaration under 37 CFR 1.132 filed by Raymond Kaempfer is insufficient to overcome the rejection of claims based upon 112 first paragraph enablement as set forth in the last Office action because: of the same reasons as set forth under the response to the argument against the 112 written description and for the reasons in the 112 enablement rejection.

Applicant's arguments, see paper no. 20, filed 5/5/03, with respect to the rejection(s)of claim(s) 2, 8-9, and 11 under 112 second paragraph have been fully considered and are persuasive in view of the amendment to the claims and the cancellation of claim 2. Therefore,

the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claim 21.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 21, 27, and 48-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the limitation "said cis-acting element" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 recites the limitation "The host cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 48 and 49 recites the limitation "an expression vector according to claim 23". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

Applicant's arguments, see paper no. 20, filed 5/5/03, with respect to 102(b) rejection as being anticipated by Pennica have been fully considered and are persuasive. The rejection of claim 1 has been withdrawn because of the amendment "does not comprise a full-length coding region" to the claim.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al., (GenBank Accession No. T29839, US National Library of Medicine, Bethesda, MD, Sept. 6, 1995, accessed by PTO on 7/9/03.). Adams teaches a nucleotide sequence (248 base pairs, dbEST ID: T29839) with 99.0% identity to SEQ ID NO: 1 and 100% identity to SEQ ID NO: 2. At base pair 122 of the sequence taught by Adams there is a N that makes the sequence 99.0% identically to SEQ ID NO: 1. However, N could be any nucleotide (A, G, C, or T) and that would make one of the four possible sequences 100% identical to SEQ ID NO: 1.

Applicant's arguments with respect to claims 1-6 have been considered but are moot in view of the new ground(s) of rejection.

Claims 7-9 remain and claims 11, 13, 14, 21, 23, 24, 25, 27, 28, 29, 30, 31, 48 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Jarrous et al. (IDS, Mol. Cell. Biol., Vol. 16, 1996, pp. 2184-2822). Jarrous discloses a vector comprising the TNF-alpha gene including the 3' untranslated region (UTR), which reads on a cis-acting nucleotide sequence of the present application a carrier (salmon sperm) and a host cell line transfected with said vector (see pages 2817 and 2820). Jarrous further teaches that the trans-acting factor for the sequence is PKR (page 2814).

Applicants' arguments filed 5/5/03 have been fully considered but they are not persuasive. The claims read on the vector taught by Jarrous. The claims do not exclude the vector taught by Jarrous. The applicants have not provided factual evidence that the human TNF-alpha gene used by Jarrous does not encode a 3' UTR region. One skilled in the art would

understand that the TNF-alpha gene contains a 3' UTR (See Alberts et al., Molecular Biology of the Cell, 3rd edition, Garland Publishing, New York, 1994, Figure 9-84).

In addition, with respect to the argument that Jarrous does not teach the cis-acting nucleotide sequence located in the 3'UTR of the human TNF-alpha gene, MPEP 2112 states, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." This is the case here. Jarrous teaches the claimed invention and the claimed DNA construct does not exclude the vector taught by Jarrous.

Conclusion

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER